AD NUMBER

AD046025

CLASSIFICATION CHANGES

TO: unclassified

FROM: confidential

LIMITATION CHANGES

TO:

Approved for public release, distribution unlimited

FROM:

Distribution authorized to U.S. Gov't. agencies and their contractors; Administrative/Operational Use; May 1953. Other requests shall be referred to Commanding Officer, Chemical Corps, Army Chemical Center, MD.

AUTHORITY

31 May 1965, DoDD 5200.10; EA D/A ltr, 6 Oct 1972

AD NUMBER

AD046025

CLASSIFICATION CHANGES

TO

confidential

FROM

secret

AUTHORITY

31 May 1956, DoDD 5200.10

Copy No. 10

AD 46025

S-13484

[redacted]

Task 3. Analogs of Tetrahydrocannabinol

for

Chemical Corps Procurement Agency

Contract No. DA 18-108-CML-4564
Progress Report
from
April thru May, 1953

[redacted]

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

Bi-Monthly Report No. 5

on

[redacted]

TASK 3

for

Chemical Corps Procurement Agency

Contract No. DA18-108-CML-4564

Period Covered: April through May, 1953

Written by: D. E. Winkler

Participants: D. D. Campbell
D. E. Winkler
R. J. Patten

Approved: R. R. Whetstone
W. E. Vaughan

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

TABLE OF CONTENTS

Abstract

The preparation of Adams' most active tetrahydrocannabinol analog (Formula I, R = 1,2-dimethylheptyl) has been delayed at the next to the last step due to the low yield of the pyrone.

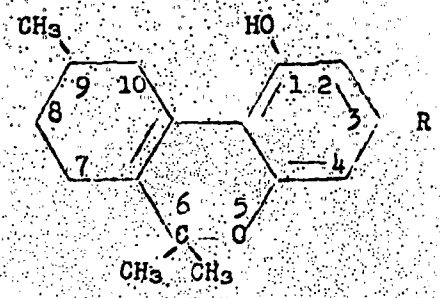
Work on the preparation of a compound having an amino group in the alkyl side chain (Formula I, R = 2-aminoethyl) has been started.

The preparation of analogs with nitrogen or sulfur in the five position via 3-amino-5-amyl phenol has been delayed awaiting the development of a satisfactory process for converting amyl-3,5-dihydroxybenzene to the desired amino compound. In the meantime, 1-hydroxy-3-n-amyl 9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone (Formula 11) has been prepared and efforts are being made to convert this pyrone to a nitrogen analog.

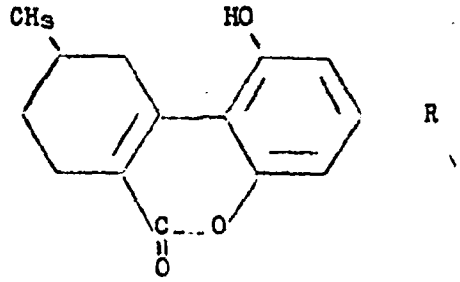
Analogs of Tetrahydrocannabinol

Changes in Alkyl Groups

The structures of tetrahydrocannabinol (I, R = n-amyl) and of the pyrone (II, R = n-amyl) mentioned in the abstract are given below for reference.



I

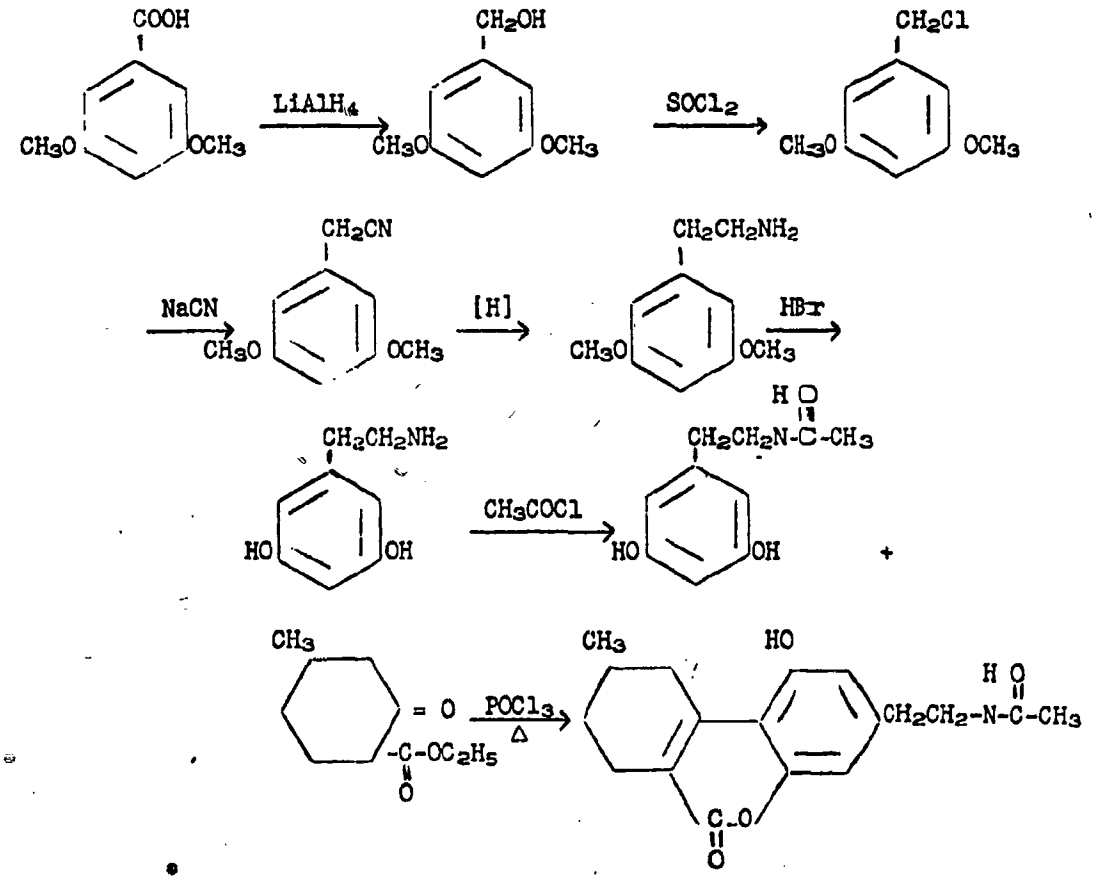


II

The preparation of the second[a] and most active of Adams' compounds in which the alkyl group (R in Formula I) is 1,2-dimethylheptyl is at the stage of the pyrone (I, R = 1,2-dimethyl heptyl) which is the next to the last step. This pyrone which is prepared by condensing 2-(3,5-dihydroxyphenyl)-3 methyloctane with ethyl 5-methylcyclohexanone-2-carboxylate[b] is being obtained in very low yields. Several runs have been made in which the reflux times for the condensation step were varied, but the best yield has been only 38% to a once recrystallized product which melts about twenty degrees low. Adams[c] reports a yield of 24%.

A compound in which the alkyl group (R in Formula I) will be 2-aminoethyl ($-CH_2CH_2NH_2$) is in process of being prepared by the following proposed route, starting with 3,5-dimethoxybenzoic acid whose synthesis has been described in a previous report.[d]

a) Winkler, D. E., Progress Report 4 (1953).
b) Winkler, D. E., Progress Report 2 (1952) and 4 (1953).
c) Adams, R., MacKenzie, S., and Loewe, S., J Am Chem Soc 70, 664 (1948).
d) Winkler, D. E., Progress Report 2 (1952).



The amide can be hydrolyzed to the amine and then the pyrone can be reacted with excess methyl magnesium iodide to produce the pyran (Formula I, R = 2-aminoethyl).

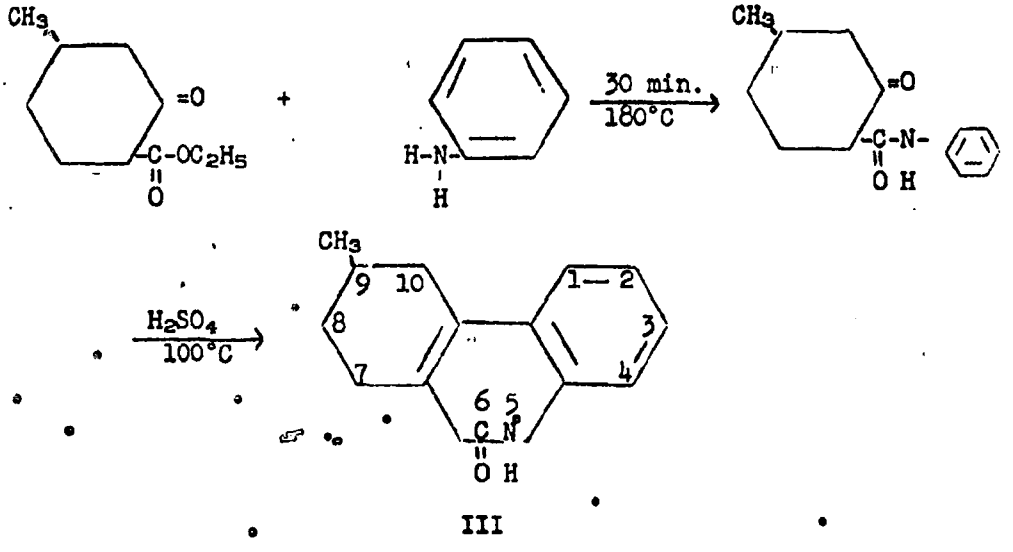
Nitrogen and Sulfur Analogs

The preparation of tetrahydrocannabinol analogs with nitrogen or sulfur in the five-position (Formula I) is being pursued by several routes. One route proposed in the last report[a] which involved the preparation of 3-amino-5-amylphenol and the condensation of this material with ethyl 5-methyl-cyclohexanone-2-carboxylate has been delayed due to our inability to prepare the 3-amino-5-amylphenol from amyl-3,5-dihydroxybenzene. Although test runs with 3,5-dihydroxytoluene had given an 82% yield of the desired amino hydroxy toluene when following the directions of Bean and Donavan[b] for

a) Winkler, D. E., Progress Report 4 (1953).
b) Bean, F. R., and Donavan, T. S., (to Eastman Kodak Co.), U. S. Patent 2,376,112 (1942).

resorcinol, the amyl-3,5-dihydroxybenzene under similar conditions gave only 3-5% yields of the desired compound with a high conversion to what is probably the secondary amine, i.e., bis(3-amyl-5 hydroxyphenyl) amine. It was felt that this may have been due to the lower water solubility of the amyl-3,5-dihydroxybenzene; so dioxane was added to give a homogeneous solution, but this did not improve the results. Under similar conditions using dioxane solvent, 3,5-dihydroxy toluene had been found to give a 50% yield of the desired amino compound. A few runs were made with the available hexylresorcinol (hexyl-2,4 dihydroxybenzene) and this was also found to give low yields of primary amino compounds.

To aid in establishing the structure of the product to be obtained from the condensation of 3-amino-5-amylphenol with ethyl 5-methyl-cyclohexanone-2-carboxylate, aniline and ethyl 5-methylcyclohexanone-2-carboxylate were condensed according to the method used by Sen and Basu[a] for condensing ethylcyclohexanone-2-carboxylate with aniline. The equation for the reaction may be written as follows.



III

The product, 9-methyl-7,8,9,10-tetrahydrophenanthridone melts sharply at 265°C.[b]

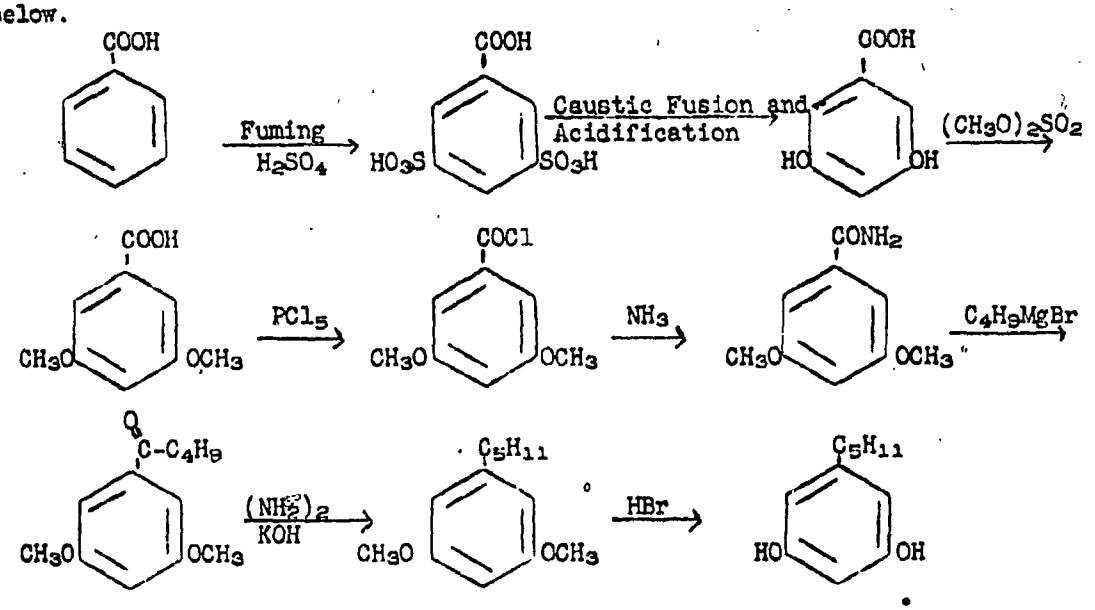
3-Amino-5-hydroxytoluene has also been condensed with ethyl 5-methyl-cyclohexanone-2-carboxylate to give a material which melts with decomposition at 272-3°C. From this material we hope to be able to determine by spectroscopic methods whether the condensation took place through the amino or hydroxyl group. Analyses are pending.

Other methods which have been tried for the preparation of nitrogen or sulfur analogs start with the pyrone (II, R = n-amyl).

a) Sen, K., and Basu, U., J Indian Chem Soc 6 309 (1929).
b) Analyses calc'd for $C_{14}H_{15}ON$: N, 6.57
Found : N, 6.4

A typical reaction of α-pyrones is their conversion to pyridones by reaction with ammonia. Heating (II) with excess ammonia in alcohol for two hours at 200°C produced very little reaction as indicated by the melting and mixed melting point of the product recovered on evaporation of the alcohol. When (II) is refluxed for only a few minutes with alcoholic KOH, the ring is opened for a water soluble compound is formed (the pyrone is not soluble in aqueous alkali at room temperature). Upon acidifying the ring is closed and the pyrone can be recovered. Since KOH is able to open the ring, another amination run was made using alcoholic ammonia containing a small amount of KOH. After two hours at 200°C the pyrone (mp 175-6°C) was converted to a viscous oil which is being worked up.

The synthesis of amyl-3,5-dihydroxybenzene, which is an intermediate in the work on nitrogen and sulfur analogs, has been accomplished by the general method of Suter and Weston.[a] The sequence of reactions is given below.

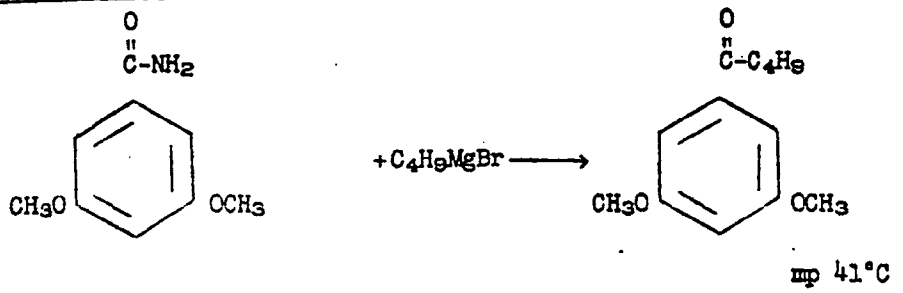


Because of modifications in the last three steps procedures for them are given in the appendix.

a) Suter, C. M., and Weston, A. W., J Am Chem Soc, 61 232 (1939).

APPENDIX

3,5-Dimethoxyphenyl Butyl Ketone, $C_{13}H_{18}O_3$



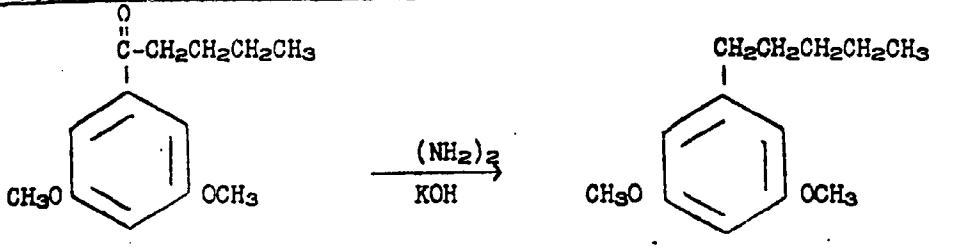
mp 41°C

To a Grignard solution prepared from 95 g (4.0 moles) of magnesium and 548 g (4.0 moles) of n-butyl bromide in 1200 ml of ether there was added 181 g (1.0 mole) of crude 3,5-dimethoxy benzamide (mp 132-6°C)[a] in about ten minutes while cooling to prevent excessive boiling. While maintaining boiling conditions, the ether was replaced with 1200 ml of anhydrous benzene to a kettle temperature of 75°C. Refluxing was continued for five hours. The addition complex was decomposed by adding 260 ml of 96% H_2SO_4 in 1500 ml of water at 0-10°C and then warming to 60°C. After washing, the product was distilled through a Claisen head at 140-146/1 mm. The crude product melted at 32-35°C, and when purified at 41°C, Asahina and Nogami[b] report 42-3°C. The yield was 200 g or 90%.

Analyses calc'd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.17
Found: C, 69.9; H, 8.2

a) Suter, C. M., and Weston, A. W., J Am Chem Soc 61, 232 (1939) report purified material to melt at 146°C.
b) Asahina, Y., and Nogami , H., Ber 68, 1500 (1935).

Amyl-3,5-Dimethoxybenzene, $C_{13}H_{20}O_2$



bp 110-120°C/1 mm

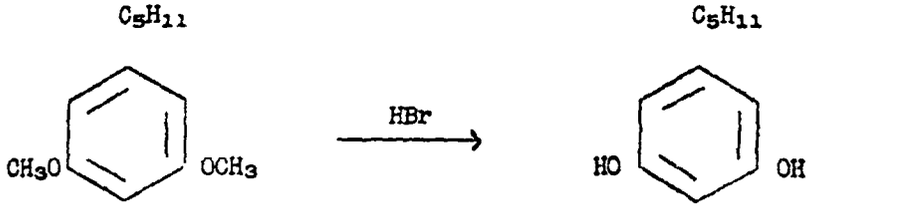
To a solution of 135 g of KOH in 1350 ml of diethylene glycol there were added 222 g (1.0 mole) of crude 3,5-dimethoxyphenyl butyl ketone and 54 g of 95+% hydrazine. The solution was heated rapidly to 140°C, then slowly to 175°C over a period of three hours with distillation of water and held at 175-180°C for one hour. Total gas evolution was 0.86 ft.^{3} which is the theoretical amount. The glycol solution was diluted with an equal volume of water and extracted with toluene. The extract was washed and distilled through a Claisen head to give a product boiling at 110-120°C/1 mm. The yield was 169 g or 81%. Asahina and Nogami[a] report a boiling point of 114°C/2 mm.

Analysis calc'd for $C_{13}H_{20}O_2$: C, 75.0; H, 9.68
Found: C, 76.2; H, 9.9

a) Asahina, Y., and Nogami, H., Ber 68, 1500 (1935).

S-13484

Amyl-3,5-Dihydroxybenzene, $C_{11}H_{16}O_2$



mp 28-29°C ex toluene

To a kettle provided with a reflux condenser there were charged 168 g (0.81 mole) of a crude 3,5-dimethoxy amyl benzene 1550 ml of acetic acid and 520 ml of 48% hydrobromic acid. The contents were refluxed five hours and then poured into a cooled solution of 1100 g of sodium hydroxide in 3 l of water. The alkyl resorcinol in the still acid solution was taken up in ether and then the ether was extracted with 120 g of sodium hydroxide in 1500 ml of water. The product was sprung with acid, taken up in ether, washed and distilled. The product boiled at 148-154°C/1 mm and solidified at room temperature. The yield was 128 g or 88%. Repeated recrystallization from water gave a product melting at 27-28°C on an aluminum block. From toluene the product melted at 28-29°C. Asahina and Nogami[a] claim amyl-3,5-dihydroxybenzene contains one mole of water when recrystallized from water and melts 40-41°C.

Analysis calc'd for $C_{11}H_{16}O_2$: C, 73.3; H, 9.0
Found on distilled product: C, 73.0; H, 9.2

a) Asahina, Y., and Nogami, H., Ber 68, 1500 (1935).